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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,724	08/31/2001	Xu Cao	D6106D	2798

7590 10/22/2003

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EXAMINER	
MCKELVEY, TERRY ALAN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 10/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/943,724	CAO ET AL.	
	Examin r	Art Unit	
	Terry A. McKelvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *6-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-5, drawn to over-expression of Smad1, transcription factor of Hoxc-8, and BMP-responsive gene osteopontin, in the reply filed 2/5/03 is acknowledged.

Claims 6-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed 2/5/03.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when

the reference is to a prior application of a CPA assigned the same application number.

In the instant case, the reference to the provisional application is no longer in the first sentence due to the inclusion of the claim to priority to 09/286,682. Amending the specification to replace the two separate priority statements with one combined priority statement would be remedial.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the *Wands* factors (MPEP 2164.01(a)). These include: nature of the invention, the state of the prior art, the predictability or lack thereof in the art,

the amount of direction or guidance present, the presence or absence of working examples, the quantity of experimentation necessary, the relative skill levels of those in the art, and the breadth of the claim. The most relevant Wands factors for evaluating the enablement of the instant rejection are discussed below.

1. Nature of the invention. The claimed invention is drawn to a method of stimulating bone formation in an individual comprising inducing an interaction between Smad1 and a homeobox-containing transcription factor (elected Hoxc-8), wherein said interaction induces a BMP-responsive gene (elected osteopontin) which produces osteoblast and/or chrondroblast differentiation thereby stimulating bone formation. The claimed method reads on any method of inducing the interaction, which includes not only the three general methods indicated in claim 2: phosphorylation of Smad1, mutation of the homeobox-containing transcription factor, and overexpression of Smad1, but also other unspecified methods such as administration of compounds (i.e., agonists) that increase the interaction, and administration of compounds that cause phosphorylation of Smad1, that cause mutation of the transcription factor, or that cause overexpression of Smad1 (e.g., specific antisense molecules). The use of gene therapy to increase expression of Smad1 is also encompassed by the

claimed invention. The claimed invention is very broad encompassing many very different methods with only the target, increasing the claimed interaction, in common. The claimed invention thus is very complex, especially since the invention is used to treat various complex, unspecified bone diseases.

2. Unpredictability of the art. The arts of stimulating bone formation in an individual and regulating disease (the only way of using the claimed method) are unpredictable. The ability to target an inducing drug with the specificity required, in the instant case, such that only bone matrix gene expression is induced, and only in bone tissue, has not been demonstrated and is highly unpredictable. The specification must teach one skilled in the art how to make and use an invention without undue experimentation. The regulation at issue requires engagement of cellular receptors and phosphorylation of receptor associated signal transduction proteins (Smads) which subsequently translocate to the nucleus. In the nucleus, such proteins de-repress gene transcription through specific interaction with homeobox-containing transcription factors (Hoxc-8). Without a complete definition of the cell types expressing the appropriate Smad protein and Hox protein, and specific targeting of those cells by the agents that induce the interaction as claimed, one would expect that the agents would

not reach the target cells in an effective concentration given that the vast majority of cells in the individual are not bone-generating cells. One must conclude that the arts of stimulating bone formation and using it to regulate diseases in individuals are unpredictable, for even one of the methods encompassed by the claimed invention, let alone the broad scope, drawn to very different methods, encompassed by the claims.

Caldwell is cited to show the unpredictability in the art concerning how to make and use a drug based upon a compound with a demonstrated in vitro activity. Caldwell teaches that drug action is the result of interaction with target sites, for both desired and undesired actions, modulated by the transfer processes, the pharmacokinetic variables of absorption, distribution, metabolism and elimination, by which the drug enters and leaves the body. This reference teaches that there is far more inter- and intraspecies variation, in animals and humans, in the factors influencing the nature and extent of internal exposure, than in the sensitivity of drug targets and this pharmacokinetic variability is the cause of major problems in drug development. Caldwell also teaches that failure to take these pharmacokinetic defects, including poor absorption, very short or very long half-life, enzyme induction and high first pass effect, into consideration can cause expensive delay and/or

failure during development. This reference thus shows that drug development is very unpredictable, requiring the consideration of many unpredictable factors in determining how to make and use the drug. These very necessary, but unpredictable factors are not taught in either the art or the specification for the specific administration of the claimed composition in vivo for disease treatment, the only intended use for the claimed pharmaceutical compositions. Thus, Caldwell shows that in the absence of much additional information concerning in vivo effects, any agent that is found to increase the claimed interaction in vitro would be unpredictable when administered in vivo to affect the same biological process as seen in vitro.

3. State of the art. The arts of stimulating bone formation in an individual and regulating disease in an individual, at the time of the applicant's invention, were poorly developed. This is especially true with regard to the use of inducing a particular interaction among the almost infinite number of different interactions in a large group of cells in a complex organism, such that a sufficient number of the correct cells (and not too many of the incorrect cells) are affected so as to have a significant effect on treating a disease by stimulating proper bone formation. The state of the arts of stimulating bone formation and regulating disease in an

individual remain underdeveloped, and extensive unpredictable experimentation and discovery will be required before any successful reduction to practice is demonstrated for even one of the methods encompassed by the claimed invention, let alone the broad scope, drawn to very different methods, encompassed by the claims.

4. Number of working examples. Applicants do not provide any working examples of the stimulation of bone formation in an individual, nor do they provide any working examples of the treatment of any disease in any individual or model organism. There aren't even prophetic teachings of how either of these goals might be achieved. In fact, applicants do not provide a prophetic teaching as to how they envision stimulating bone formation in an individual, as to how they envision regulating a disease, or even how regulation of that disease is to be specifically accomplished. The methods provide no steps that indicate how the interaction between a Smad1 protein and a homeobox-containing transcription factor is to be induced, how tissue specificity is to be achieved, or even what dose of the inducer is appropriate to effect the desired response.

5. Amount of guidance presented by applicants. Applicants present no actual or even prophetic guidance as how to their claimed invention could be practice in humans or any other

organism. A significant level of guidance in the specification is necessary to enable one of ordinary skill in the art to practice the claimed invention due to the absence of such guidance in the art and the unpredictability in the art. If compounds are envisioned as inducers of an interaction between Smad1 and a homeobox-containing transcription factor, then the various factors specific to the administration of each compound must be empirically determined, as discussed by Caldwell cited above. There are no teachings in the instant specification or the prior art regarding induction of a specific association between two proteins such as Smad1 and a transcription factor as a means for stimulating bone formation. Although the instant specification demonstrates an induction of osteoblastic differentiation in vitro, no such demonstration is attempted in vivo, in any animal model. Such a demonstration would require unpredictable trial and error experimentation and would not be considered by one of skill in the art as routine, given the unpredictable parameters that must be determined for success in this complex area.

6. Scope of the claims. As indicated above, the claimed invention encompasses any method of inducing the interaction, including many very different compounds and method steps, each

of which would have the unpredictability and the problems indicated above.

7. Level of skill in the art. The level of skill in the arts of stimulating bone formation in individuals and of regulating diseases in individuals is underdeveloped. The challenges, and the unpredictable ways of overcoming those challenges in various circumstances, that remain before gene therapy (which is encompassed by the elected method of overexpression of Smad1) is successfully reduced to routine practice are well documented, including by Anderson (4/30/98) and Verma et al (9/18/97), as are the challenges of appropriate tissue targeting using drugs (Langer) and formulating a bioactive compound into a drug that can be successfully administered to treat disease (Caldwell). Thus, the level of skill in the art of stimulating bone formation by inducing an interaction (presumably by administering a compound) and using that induction to treat disease remains relatively low and underdeveloped.

Given the above analysis of the factors which the courts have indicated are critical in determining whether a given invention is enabled, it must be considered that the skilled artisan would have to practice undue and excessive unpredictable experimentation in order to practice the claimed invention given

the complex nature of the invention, the high degree of unpredictability in the art, the underdeveloped state of the art, the lack of working examples or art-recognized animal models showing induction of the claimed interaction to stimulate bone formation for treatment of disease, the complete lack of any real, specific guidance in the specification and the art, the broad scope of the claimed invention encompassing many different methods, and the underdeveloped skill in the art.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is drawn to a method of stimulating bone formation in an individual comprising inducing an interaction between Smad1 and a homeobox-containing transcription factor (elected Hoxc-8), wherein said interaction induces a BMP-responsive gene (elected osteopontin) which produces osteoblast and/or chrondroblast differentiation thereby stimulating bone formation. The claimed method reads on any

method of inducing the interaction, which includes not only the three general methods indicated in claim 2: phosphorylation of Smad1, mutation of the homeobox-containing transcription factor, and overexpression of Smad1, but also other unspecified methods such as administration of compounds (i.e., agonists) that increase the interaction, and administration of compounds that cause phosphorylation of Smad1, that cause mutation of the transcription factor, or that cause overexpression of Smad1 (e.g., specific antisense molecules). The use of gene therapy or protein therapy to increase expression of Smad1 is also encompassed by the claimed invention. The claimed invention is very broad genus of methods encompassing many very different methods with only the target, increasing the claimed interaction, in common.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In the instant case, the only factor present in the claims is drawn to the induction of the claimed

interaction, which is actually just a description of the target that is to be affected, without any description of the compounds or the method steps to affect that target. Beyond the fact that the claimed invention reads generally on administration of Smad1 protein or nucleic acid to induce the interaction as claimed, the specification fails to describe the structure of even one non-Smad1 compound which can be used to induce the interaction as claimed. There is no description of what steps or compounds are to be used to phosphorylate Smad1 in vivo, and there is no description of how to mutate a homeobox-containing transcription factor in vivo, so as to achieve any significant benefit. There is no description of the method steps to be performed in order to use Smad1 proteins or nucleic acids to induce the interaction as claimed in order to achieve a significant result.

Accordingly, in the absence of sufficient recitation of distinguishing characteristics of the compounds and methods to practice the claimed invention, the specification does not provide adequate written description of the claimed genus. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See

page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of compounds used to induce the interaction as claimed, nor can the skilled artisan envision the specific method steps to practice the claimed invention, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification of the compounds to be used in the method steps. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18USPQ2d 1016. Because the claimed methods appear to rely upon compounds to achieve the induction of the claimed interaction, the compounds themselves are needed for the claimed invention.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of

written description for that broad class. The specification provided only the bovine sequence.

Therefore, the full breadth of the claims does not meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The use of "Smad1" renders the claims vague and indefinite because the metes and bounds of the proteins encompassed by the term are unclear in light of the specification. The specification sets forth its own definition of Smad1: "As used herein, the term "Smad1" shall refer to any proteins that are homologous to Drosophila mothers against DPP or MAD protein." The metes and bounds of the proteins encompassed are unclear

because there is no clear art-recognized definition of "homologous" in this context and the specification fails to set forth a clear indication of the metes and bounds of the term.

Conclusion

No claims are allowed.

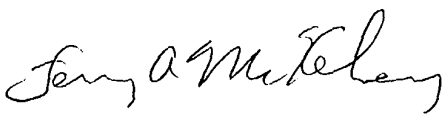
Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is 703-872-9306. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning rejections or other major issues in this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 7:30 AM to about 6:00 PM. A phone message left at this number will be

responded to as soon as possible (i.e., shortly after the examiner returns to his office).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

October 19, 2003